



Diabetes and Dementia

Mario Barbagallo* and Ligia J. Dominguez

Geriatric Unit, Department DIBIMIS, University of Palermo, Italy

*Corresponding author: Mario Barbagallo, UOC di Geriatria e Lungodegenza, AOUP Azienda Universitaria Policlinico, University of Palermo, Italy, Tel: +390916552885, Fax: +390916552952, E-mail: mario.barbagallo@unipa.it

Abstract

Persons with type 2 diabetes mellitus (DM2) have an increased incidence of cognitive decline and dementia. An increased cortical and subcortical atrophy has been found after controlling for vascular disease and inadequate cerebral circulation. A possible role of insulin resistance and hyperinsulinemia has been suggested to mediate the link between DM2 and Alzheimer's Disease (AD). Altered insulin signaling may contribute to AD biochemical and histopathological lesions. Both hyperglycemia and hypoglycemia may contribute to cognitive decline in DM2. Recurrent symptomatic and asymptomatic hypoglycemic episodes have been suggested to cause subclinical brain damage, and permanent cognitive impairment. Future trials are needed to clarify if cognitive decline may be prevented by an adequate metabolic control, insulin-sensitizing agents and avoiding hypoglycemia.

Keywords

Dementia, Alzheimer's disease, Type 2 diabetes, Aging, Cognitive decline, Insulin, Insulin resistance, Hypoglycemia, Hyperglycemia.

Type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD) are among the fastest growing epidemics of the third millennium, which are both associated with aging of the population [1,2]. DM2 is characterized by impairment in insulin action, insulin resistance and hyperinsulinemia. AD is pathologically distinguished by the presence of several hallmarks including neuronal loss, deposits of amyloid beta (senile plaques), intracellular neurofibrillary tangles composed of aggregated hyperphosphorylated *tau* proteins in brain, proliferation of astrocytes, and activation of microglia, associated with mitochondrial dysfunction and alterations in neuronal synapses [3]. Most studies have suggested that the deposit of the toxic amyloid-beta peptide (amyloid cascade hypothesis), may be a triggering factor contributing to the pathogenesis of AD.

DM2 is associated with several and important changes in cognition, and it has been strongly associated with an increased risk of developing dementia [4-6]. Thus, the incidence of dementia and the risk of developing AD are significantly higher in persons with DM2 than in those without diabetes [7-9]. In a community-based controlled study, frank diabetes (35%) or glucose intolerance (46%) was present in up to 80% of patients with AD [10], and longer diabetes duration has been associated with a higher risk for developing dementia [6,11,12]. The areas of cognitive functions that have been suggested to be mainly affected in persons with diabetes are attention, learning and memory, mental flexibility, psychomotor efficiency,

speed and executive functions [13,14]. Not only frank dementia, but also mild cognitive impairment (MCI) is associated with DM2, as well as an accelerated progression from MCI to dementia [15]. Dementia is the most common comorbidity in persons with diabetes in nursing homes [16].

Several studies on the cerebral structure of patients with diabetes have evidenced increased cortical and subcortical atrophy (besides increased leukoaraiosis and cerebrovascular disease), which were associated with impaired cognitive performance [17,18]. Insulin itself and insulin resistance have been suggested as mediators of AD-type neurodegeneration. It has been proposed that AD may be termed as "type 3 diabetes", indicating that AD may represent a form of diabetes that selectively involves the brain with molecular and biochemical features that overlap with diabetes mellitus [19].

Insulin has significant neurotrophic properties in the brain. The hormone is rapidly transported to the level of the central nervous system through the blood-brain barrier by a transport mechanism mediated by insulin receptors, mainly localized at the level of the hippocampus, entorhinal cortex and frontal areas (areas known to be involved in memory and learning). Insulin is also involved in the production of important neurotransmitters such as acetylcholine and norepinephrine. A state of chronic hyperinsulinemia, as it occurs in insulin-resistance conditions and in DM2, may determine a down-regulation of the insulin receptors at the blood-brain barrier, thus reducing the transport of insulin in the brain. Insulin metabolism is linked to the deposition of precursors of amyloid in the brain. The amyloid precursor protein (APP) is a transmembrane protein consisting of 770 amino acids; it is known to be the precursor of the amyloid beta involved in the pathogenesis of AD. Whereas insulin is a neurotrophic factor at moderate concentrations, hyper-insulinemia with elevated concentrations of insulin in the brain may be associated with reduced amyloid-beta clearance due to competition for their common and main degrading mechanism — the "Insulin-Degrading Enzyme" (IDE).

Insulin is degraded by the IDE, which is also involved in the metabolism and degradation of amyloid beta. Thus, IDE competitively degrades both insulin and amyloid-beta peptide in the AD brain [20]. Since IDE is much more selective for insulin than for amyloid beta, a condition of hyperinsulinemia may deprive amyloid-beta of its main clearance mechanism, favoring its accumulation in the brain, and its consequent neurotoxic effects [21]. Hyperinsulinemia and insulin resistance have been associated with more hippocampal and amygdalar atrophy on MRI in persons with DM2 when compared

Citation: Barbagallo M, Dominguez LJ (2015) Diabetes and Dementia. Int J Diabetes Clin Res 2:038

Received: July 26, 2015; **Accepted:** July 31, 2015; **Published:** August 03, 2015

Copyright: © 2015 Barbagallo M. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

to matched non-diabetic controls, regardless of vascular pathology [13,17].

Plasma glucose itself is a risk factor for cognitive dysfunction and dementia; both higher (hyperglycemia) and lower (hypoglycemia) levels of glucose may have deleterious effects on the brain. In a prospective, community-based cohort study, higher plasma glucose concentrations were associated with an increased risk of dementia in populations with and without diabetes [22], and the risk of incident dementia increased in diabetic and in non-diabetic persons according to the average glucose concentrations during the preceding 5 years [22]. Hyperglycemia and hyperinsulinemia may accelerate brain aging also by inducing *tau* hyperphosphorylation and amyloid oligomerization, as well as by leading to widespread brain microangiopathy. Persons with diabetes also develop accelerated leukoariosis (white matter high-intensity lesions) [23].

The effect of diabetes treatment and glycemic control on dementia risk are less clear. It has been suggested that glycemic control may have a role in preserving cognitive performance among patients with DM2. Using baseline cognitive measures collected in the Memory in Diabetes (MIND), sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the authors found that a 1% higher glycated hemoglobin A1c (HbA1c) value was associated with a significant lower performance and memory score test in patients with diabetes [24].

HbA1c was also identified as an additional risk factor for a greater rate of brain atrophy. Significant differences in brain atrophy rates measured by MRI were found by quartiles of HbA1c levels [25]. The hypothesis that an inadequate glucose control may be associated with worsening cognitive function is confirmed by the inverse relationship found between serum HbA1c and working memory, executive functioning, learning, and complex psychomotor performance, in diabetic subjects [26,27].

However, an excessively tight glycemic control in older persons with DM2, and its related increased risk of hypoglycemia, also has been associated with deleterious effects on cognitive function [28]. Hypoglycemia may be undetected and current symptoms may include alterations of cognitive function, such as difficulty in concentrating and drowsiness, among others. Recurrent symptomatic and asymptomatic hypoglycemic episodes have been suggested to cause subclinical brain damage, and permanent cognitive impairment [29]. Among DM2 patients, a history of severe hypoglycemic episodes is associated with a greater risk of dementia [30]. A bidirectional association between hypoglycemia and dementia has been suggested [31]. During a 12-year follow-up period, participants who experienced at least one hypoglycemic event had a 2-fold increased risk for developing dementia. On the other side, DM2 subjects with dementia had a threefold increased risk for having a subsequent hypoglycemic event compared with those without dementia [31]. This is easily understandable, since many hypoglycemic episodes may be due to errors in drug self-administration in demented patients. Unrecognized hypoglycemia can occur at all ages but is particularly harmful in older persons, in whom hypoglycemic symptoms and adrenergic signs may be attenuated. Among drugs, sulphonylureas have a particular high risk to cause hypoglycemic episodes, while drugs that cause lower postprandial glucose excursions and minor risk of hypoglycemia may help in preventing cognitive decline in older diabetic persons [32].

It has been also suggested that the shared pathogenesis between type 2 diabetes and dementia ("Type 3 diabetes") may raise the possibility that insulin-sensitizing agents might be useful in treating the insulin-resistant brain state seen in AD [33]. This data needs to be confirmed by future trials.

In conclusion, there are convincing epidemiological and physiopathological evidences showing an increased risk of dementia in people with diabetes. Cerebrovascular alterations, insulin action, insulin resistance, altered amyloid metabolism, chronic hyperglycemia, and recurrent hypoglycemic episodes, may all play

a major role. Future trials are required to clarify the mechanistic link and to address the question whether cognitive decline may be prevented by an adequate metabolic control, and the possible role of insulin-sensitizing agents. Clinicians treating older persons with diabetes should start to routinely search for cognitive impairment as well as they search for other common complications of diabetic disease. We believe that there is sufficient evidence to include cognitive evaluation in future diabetic guidelines.

References

1. Barbagallo M, Dominguez LJ (2014) Type 2 diabetes mellitus and Alzheimer's disease. *World J Diabetes* 5: 889-893
2. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, et al. (2002) Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol* 59: 1737-1746.
3. Mattson MP (2004) Pathways towards and away from Alzheimer's disease. *Nature* 430: 631-639.
4. Akomolafe A, Beiser A, Meigs JB, Au R, Green RC, et al. (2006) Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. *Arch Neurol* 63: 1551-1555.
5. Wrihten SA, Piroli GG, Grillo CA, Reagan LP (2009) A look inside the diabetic brain: Contributors to diabetes-induced brain aging. *Biochim Biophys Acta* 1792: 444-453.
6. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, et al. (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 53: 1937-1942.
7. Biessels GJ, Staekenborg S, Brunner E, Brayne C and Scheltens P (2006) Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 5: 64-74.
8. Allen KV, Frier BM, Strachan MW (2004) The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations. *Eur J Pharmacol* 490: 169-175.
9. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA and Bennett DA (2004) Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* 61: 661-666.
10. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, et al. (2004) Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes* 53: 474-481.
11. Bruce DG, Davis WA, Casey GP, Starkstein SE, Clarnette RM, et al. (2008) Predictors of cognitive decline in older individuals with diabetes. *Diabetes Care* 31: 2103-2107.
12. Bruce DG, Davis WA, Casey GP, Starkstein SE, Clarnette RM, et al. (2008) Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia* 51: 241-248.
13. Convit A (2005) Links between cognitive impairment in insulin resistance: an explanatory model. *Neurobiol Aging* 26: 31-35.
14. Kodl CT, Seaquist ER (2008) Cognitive dysfunction and diabetes mellitus. *Endocr Rev* 29: 494-511.
15. Alagiakrishnan K, Sclater A (2012) Psychiatric disorders presenting in the elderly with type 2 diabetes mellitus. *Am J Geriatr Psychiatry* 20: 645-652.
16. Gadsby R, Barker P, Sinclair A (2011) People living with diabetes resident in nursing homes--assessing levels of disability and nursing needs. *Diabetic Med* 28: 778-780.
17. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, et al. (2003) Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 46: 1604-1610.
18. Cherbuin N, Sachdev P, Anstey KJ (2012) Higher normal fasting plasma glucose is associated with hippocampal atrophy: The PATH Study. *Neurology* 79: 1019-1026.
19. de la Monte SM, Wands JR (2008) Alzheimer's disease is type 3 diabetes-evidence reviewed. *Journal of diabetes science and technology* 2: 1101-1113.
20. Qiu WQ, Folstein MF (2006) Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiol Aging* 27: 190-198.
21. Craft S, Watson GS (2004) Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol* 3: 169-178.
22. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, et al. (2013) Glucose levels and risk of dementia. *New Engl J Med* 369: 540-548.
23. J SR-F, Sa-Roriz TM, Rosset I, Camozzato AL, Santos AC, et al. (2009) (Pre) diabetes, brain aging, and cognition. *Biochim Biophys Acta* 1792: 432-443.
24. Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, et al. (2009) Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors:

-
- the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. *Diabetes Care* 32: 221-226.
25. Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, et al. (2005) Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology* 64: 1704-1711.
26. Reaven GM, Thompson LW, Nahum D, Haskins E (1990) Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care* 13: 16-21.
27. Munshi M, Grande L, Hayes M, Ayres D, Suhl E, et al. (2006) Cognitive dysfunction is associated with poor diabetes control in older adults. *Diabetes Care* 29: 1794-1799.
28. Dominguez LJ, Paolisso G, Barbagallo M (2010) Glucose control in the older patient: from intensive, to effective and safe. *Aging Clin Exp Res* 22: 274-280.
29. Warren RE, Frier BM (2005) Hypoglycaemia and cognitive function. *Diabetes Obes Metab* 7: 493-503.
30. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr and Selby JV (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 301:1565-1572.
31. Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, et al. (2013) Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern Med* 173: 1300-1306.
32. Abbatecola AM, Rizzo MR, Barbieri M, Grella R, et al. (2006) Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. *Neurology* 67: 235-240.
33. Shaw K (2013) 'Type 3 diabetes': linking a brain insulin-resistant state with dementia and Alzheimer's disease. *Pract Diabetes* 30:102-3.